ELASTOMERIC COMPONENTS FOR THE PHARMACEUTICAL INDUSTRY

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INTRODUCTION

The primary function of elastomeric components used by the pharmaceutical industry, which includes both drugs and medical devices, is to protect and deliver. Elastomeric components are typically primary packaging components; that is, they are or may be in direct contact with the dosage form. They must neither interact with the dosage form nor allow the ingress or egress of materials. Elastomeric or rubber components typically provide the means for sealing parenteral containers of varying size and shape because of their unique physical properties. Elasticity particularly permits intimate contact between the closure and the relatively rigid surfaces of container openings. No other material known today has this same unique property. This property is primarily responsible for the ability of the closure to be pierced with a sharp device, such as a hypodermic needle, and then to reseal. This is an example of the delivery function of elastomeric components. Rubber closures are an essential component of the primary package for most parenteral or injectable products. Typical rubber components are pictured in Figs. 1 and 2.

In order to understand how rubber performs its unique "protect and deliver" function, it is necessary to know how rubber is compounded and manufactured.

RUBBER COMPOUNDS

Rubber, like all other primary packaging materials, is not inert. Any material used in the compounding of the rubber component may be leached into and/or chemically react with the dosage form. The basic materials used in the compounding of rubber components used by the drug and medical device industries are listed in Table 1. These materials, and the amounts used, are significantly different from those that may be used in industrial rubber belts, tires, and hoses where heat, abrasion, and solvent resistance are typically the main concern. More than one type of each material may be used in a rubber compound. For example, compounds containing two elastomers, such as isoprene and chlorobutyl rubber, and two pigments, such as titanium dioxide and carbon black, are very common. Compounds used for parenteral closures consist of an elastomer as the base material combined chemically and physically with other necessary rubber chemicals.

The elastomer determines most of the physical and chemical characteristics of a rubber compound. Typical elastomers are natural elastomers such as natural rubber (NR), sometimes called crepe, and synthetic elastomers such as butyl (including chlorobutyl and bromobutyl), ethylene propylene diene monomer (EPDM), and styrene butadiene rubber (SBR). A list of commonly used elastomers is shown in Table 2.

In the pharmaceutical industry, natural rubber and its synthetic analog, isoprene rubber, are normally used in products that require good physical strength or that must be able to withstand multiple punctures while maintaining seal integrity. Due the "latex sensitivity" issue, the use of natural rubber is declining. This issue is discussed in a later section. Neoprene, a halogenated form of polyisoprene, is typically used for oil-based pharmaceutical products, such as mineral oil or vegetable oil. SBR and nitrile rubber (NBR), which is used primarily for oil-based products, are specialty elastomers that are not as commonly used. Butyls and halobutyls comprise the largest segment of pharmaceutical rubber compounds, having properties that make them applicable for the packaging of many products, especially those requiring protection from moisture vapor or oxygen. Most lyophilized and powdered products require this protection, and some liquid products require protection from oxygen. EPDMs are less commonly used, though they have been selected for large intravenous (IV) stoppers. Silicones also are not often used due to their permeability to moisture vapor and oxygen as well as their relatively high cost. A list of common elastomers and their chemical structures is found in Table 3.

Curing (or vulcanizing/cross-linking) agents are chemicals used to cross-link elastomer chains into the three-dimensional (3D) network required to give a rubber component the desired elasticity. The term "vulcanization" indicates that heat is employed in the manufacturing or molding process. Common curing agents are sulfur,

Fig. 1 Typical rubber components. A) Syringe plunger. B,C,D) Sleeve stoppers. E) Abbott ADDVantage vial stopper. F) IV bag injection site. G) Serum vial stopper. H) Lyophilization vial stopper. (Photograph provided by Abbott Laboratories.)

thiurams, zinc oxide, peroxides, resins, and amines. A desirable property of pharmaceutical rubber formulations is "cleanliness," that is, that they contain materials that neither leach nor volatilize into the packaged pharmaceutical. Sulfur-cured rubber, because it requires other chemicals to effect an efficient cure, is not usually as clean as resin-, metal oxide-, or peroxide-cured formulations. The demands of the pharmaceutical industry and regulatory agencies are such that these relatively clean cure systems are becoming more common.

Accelerators reduce the cure time considerably by increasing the cure rate. They are not catalysts because they are chemically altered and, in many cases, also react as curing agents. Common sulfur-cure accelerators are amines, dithiocarbamates, sulfenamides, thiazoles, and thiurams. Some accelerators, because of their reactivity, may form toxic compounds, such as 2-(2-hydroxyethylmercapto)benzothiazole from mercaptobenzothiazole (2-MCBT), residues of which may be extractable. Accelerators that are secondary amines may form toxic nitrosamines.

Activators, which affect the efficiency of accelerators, are commonly added. Normally these are metal oxides, such as zinc oxide or stearic acid.

Fig. 2 Typical rubber syringe plungers. A) Plunger for 10-mL sterile-empty syringe. B) Plunger for sterile-prefilled dental cartridge. C) Plunger for 1mL sterile-empty syringe. D) Tip cap for Luer Tip syringe. (Photograph provided by West Pharmaceutical Services, Inc.)

Antioxidants are classified as antidegradants or age resistors. Chemically, antioxidants protect the reactive (sensitive) sites of the rubber chains against oxygen attack. Typical antioxidants are chemicals such as hindered phenols and amines. Unsaturated elastomers, such as natural rubber, require antioxidants for protection against oxidation, which causes surface cracking and loss of elasticity. Saturated elastomers, such as silicones and fluoroelastomers, are resistant to oxidation and usually require no added antioxidants. Some antioxidants are classified as antiozonants, which are designed to provide protection when high levels of reactive ozone are likely to be in the environment. A list of saturated and unsaturated elastomers is found in Table 4.

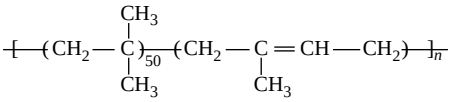
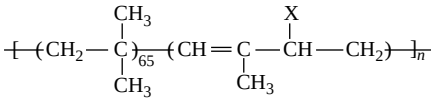
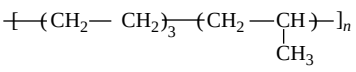
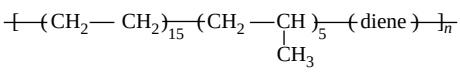
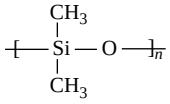
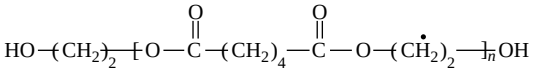
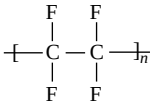
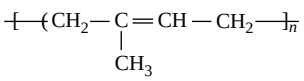
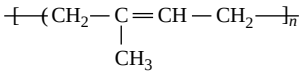
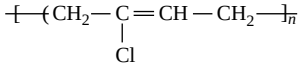
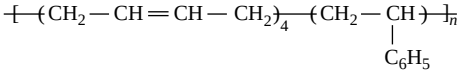
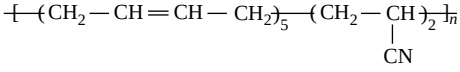
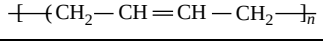
Table 1 Rubber compounding materials and their function

Material	Function
Elastomer	Base material
Curing agent	Forms cross-links
Accelerator	Affects type and rate of cross-links
Activator	Alters efficiency of accelerator
Antioxidant	Antidegradant
Plasticizer	Processing aid
Filler	Affects physical properties
Pigment	Color

Table 2 Common elastomers used in parenteral packaging components

Elastomer	% Use	Reason
Butyl/halobutyls	~80	Excellent O_2 and moisture barrier
Natural/isoprene	~10	Excellent physical properties such as reseal
EPDM	~5	Good heat resistance and surface lubricity
Nitrile and neoprene	~3	Resistance to vegetable and mineral oils
SBR	~1	Blended with isoprene/NR or halobutyls to improve physical properties
Silicone	≪1	Excellent heat resistance; poor O_2 and moisture barrier; high cost

Table 3 Chemical structures of common elastomers

Common name	Chemical name	Structure
Butyl rubber	Poly(isobutylene-isoprene)	
Halobutyl rubber[a]	Halogenated poly(isobutylene-isoprene)	
Ethylene-propylene rubber	Poly(ethylene-propylene)	
Ethylene-propylene-diene rubber	Poly(ethylene-propylene-diene)	
Silicone rubber	Polydimethylsiloxane	
Urethane rubber	Adipic acid-ethylene glycol polyester	
Fluoroelastomers	Polytetrafluorethylene	
Natural rubber	*cis*-(1.4-Polyisoprene)	
Polyisoprene rubber	*cis*-(1.4-Polyisoprene)	
Neoprene rubber	Polychloroprene	
Styrene-butadiene rubber	Poly(butadiene-styrene)	
Nitrile rubber	Poly(butadiene-acrylonitrile	
Polybutadiene	Polybutadiene	

(From Ref. 22.)
[a]X = Cl or Br.

Table 4 Saturated and unsaturated elastomers

Saturated	ASTM abbreviation	Unsaturated	ASTM abbreviation
Butyl	IIR	Natural	NR
Halobutyls (chlorobutyl and bromobutyl)	CIIR, BIIR	Isoprene	IR
Ethylene-propylene-diene monomer rubber	EPDM	Styrene butadiene	SBR
Silicone	Q	Nitrile	NBR
Urethane	U	Neoprene	CR
Fluoroelastomers	FKM	Polybutadiene	BR

Plasticizers are used in rubber compounds to assist in the mixing or molding of the rubber, to soften the final vulcanized rubber, or to add surface lubricity to the surface of the rubber component. Examples are paraffinic wax, silicone oil, paraffinic and naphthenic oils, phthalates, and organic phosphates. Silicone oil is commonly used in syringe pistons that must slide freely within a glass or plastic barrel; it also reduces the coring or fragmentation tendency of vial stoppers.

Fillers are materials that modify rubber characteristics (e.g., hardness) and improve its physical characteristics (e.g., tensile strength), in addition to reducing costs. Rubber is sometimes compounded without the use of fillers; the resultant product is called "gum rubber." Typical fillers are calcined and hydrated clays, magnesium silicate (talc), magnesium oxide, and silicas. Carbon black, a common filler used to increase the heat resistance in industrial components such as tires, is not used as a filler in pharmaceutical components but it is used in smaller amounts as a black pigment. Polynuclear aromatic (PNA) hydrocarbons are a concern with carbon blacks but the grades used by manufacturers of pharmaceutical components contain very low concentrations.

The pigments used are inorganic salts and oxides, carbon black, or organic dyes that are used for aesthetic or functional purposes (e.g., identification, designating a dosage, etc.). Typical pigments are carbon black, titanium dioxide, and iron oxide. With these three pigments white, black, red, and many shades of gray and pink can be produced. These pigments are chemically pure and stable, nontoxic, and relatively inexpensive. Other pigments such as phthalocyanines and ultramarine blue can be used for blues and greens, but their color fastness in not as good as the aforementioned pigments.

A typical thermoset rubber compound is shown in Table 5. In terms of percentage by weight, the elastomer and filler are the chief materials used, accounting typically for over 90% of a compound. However, the other "minor" materials are quite necessary in order for the compound to have the necessary chemical, physical, and toxicological properties required for a functional packaging component. For example, without the curing agent the compound would remain a physical mixture of materials that would have the consistency of chewing gum. On the other hand, materials such as pigments may be omitted from the compound with only minor consequences — i.e., the loss of the desired color.

SELECTION OF COMPOUND MATERIALS

Many materials may be used in a rubber compound; however, only a fraction of materials are acceptable in components used for the drug industry. A source of

Table 5 Typical thermoset rubber compound

Material	Percent by weight
Chlorobutyl rubber (elastomer)	52.7
Calcined clay (filler)	39.4
Paraffinic oil (plasticizer)	4.4
Titanium dioxide (pigment)	1.1
Carbon black (pigment)	0.13
Thiuram (curing agent/accelerator)	0.14
Zinc oxide (activator)	1.6
2,6-Di-tert-butyl-4-sec-butyl phenol (antioxidant)	0.53

acceptable materials is the U.S. Code of Federal Regulations (CFR). Since the CFR has no list for drug contact, the drug industry uses the CFR list designated for foods. Applicable sections of 21 CFR are as follows:

Section 175—Indirect Food Additives
Sections 177 and 178—Indirect Food Additives Polymers
Sections 182, 184, 185—Generally Regarded as Safe (GRAS) Lists
Section 177.2600—Rubber Articles Intended for Repeated Use (The primary section containing a list of materials used in rubber formulations for pharmaceutical items.)

There are some cautions with the CFR lists. First, manufacturers may not always submit materials to the Food and Drug Administration (FDA) for listing in the CFR. They may not want to take the time or incur the costs if they see only a limited market for their material in the pharmaceutical or food market. Second, some materials, such as 2-MCBT, which is not permitted by the FDA, are listed but are strongly discouraged. Finally, some materials listed in the CFR, such as food, drug, and cosmetic dyes, are really not applicable for rubber compounds used for pharmaceuticals. Many of these dyes are water-soluble and are not applicable for rubber formulations that come in contact with aqueous solutions, since the dyes could be extracted from the rubber and discolor the drug.

Component manufacturers may use materials not listed in the CFR provided that acceptable toxicity data is available to the reviewing health authority.

TYPES OF RUBBER AND THE MANUFACTURING PROCESS

Elastomeric closures for parenteral products are made from two types of elastomers or rubbers. Thermoset rubber, the most common, undergoes a chemical reaction during the molding or component-forming processing. In this chemical reaction cross-links, or bonds are inserted between the long polymer chains to form a resilient 3D network. Without these cross-links elastomeric closures would have properties resembling those of chewing gum, which is an uncross-linked rubber blended with sugar, flavors, and food coloring. The cross-linking process is not reversible. Once a closure is molded it cannot be remolded into another shape or size. Addition of heat only causes degradation or reversion of the rubber.

Another type of rubber that is used frequently is thermoplastic rubber (1, 2). Components are fabricated in a process that is similar to that used for common hard plastics, such as polyethylene or polystyrene, but the final product is an elastic material with properties otherwise equivalent to those of thermoset rubbers. No chemical reactions are involved in the processing of a thermoplastic rubber. The fabrication process consists of heating the rubber compound until it liquefies, injecting the liquid into a mold, cooling the mold, and finally removing the closure from the mold. The process is reversible. Closures can be remelted and remolded into different shapes or sizes as desired. Cross-linking in this case is not a chemical process but a physical intertwining of polymeric chains. The resulting intertwined 3D network gives thermoplastic elastomers their elasticity and resiliency.

Currently, thermoplastics account for less than 5% of the elastomeric closures for parenterals. Their limited resistance to heat deformation under stress during autoclave sterilization is the main reason for this limited use. However, thermoplastics have two advantages over thermosets. First, they are chemically less complex and therefore less prone to interact with parenteral medications, and second, they may be manufactured by a simpler and more automated process. Thermoplastic elastomers have found use in baby bottle nipples and dropper bulbs that are not typically heat sterilized under compression.

The manufacturing of rubber components for pharmaceutical applications is a multistep process with controls on each step. Fully validated processes are now common. The process is outlined in Table 6.

There are generally three molding processes used for manufacturing pharmaceutical closures: compression molding, injection molding, and transfer molding. The choice of molding method usually depends on the necessary final dimensional tolerances of the item being molded. Injection molding gives the best dimensional tolerances; however, it is usually the most expensive technique, especially as compared to compression molding. Thermoset rubbers are commonly compression or transfer molded, while thermoplastic rubbers are typically injection molded. The compression molding cycle is illustrated in Fig. 3. Sheets of molded components vary in shape from round to rectangular, and in size from 12 in. in diameter to 36 × 36 inches square, and may contain 50–10,000 components.

A recent trend in rubber component manufacturing is the production of "preprocessed" components. Components are prepared for shipment in either one of two states:

1. *Ready to Sterilize (RtS):* Typically components are washed, then rinsed with Water For Injection (WFI) to reduce bioburden and endotoxin levels, lubricated with

Table 6 Manufacturing process for rubber components for pharmaceutical use

Process step	Comment
1. Raw material specifications and testing	Tests for identity and purity
2. Weighing of batch ingredients according to DMF-filed "recipe"	Weighted to ±0.2% of nominal batch weight
3. Mixing to get homogeneous batch of material	Mixed either in an internal mixer or on an open mill
4. Testing representative samples of the mixed batch of rubber	Blend of ingredients is tested for cure characteristics; molded test piece is tested for common attributes such as durometer hardness, specific gravity, percentage ash, IR spectrum of pyrolizate, and UV spectrum of an aqueous extract.
5. Preform material by extrusion, calendering or pelletizing	Material is formed into blocks, trips, sheets or pellets for ease of handling
6. Preformed material is placed on mold or into mold feeder mechanism	
7. Molding by compression, transfer, or injection techniques	Unvulcanized mixtures of materials are shaped into the desired component by heat and pressure; chemical reaction causes cross-links to form between polymer chains
8. Trimming	Convert molded sheets of connected components into individual components
9. Washing	Remove particulate matter, and mold and trim lubricants
10. Rinsing	Reduce surface endotoxins and bioburden when WFI water is used
11. Sterilization	Only done when presterilized components are produced
12. Final QC testing	Tests for identity, dimensional measurements, and physical, chemical and biological tests
13. Packing	A counted number of components are placed in containers, usually bags made of polyethylene or Tyvek®, then sealed in cardboard cartons for shipping
14. Shipping	Cartons are grouped by lot number, palletized and shipped by truck, ship or air

silicone oil, and finally packaged in a classified area (Classes 100–10,000) in Tyvek® bags that can be steam sterilized by the drug or device manufacturer before use. Alternately polyethylene bags may be used if the end user is utilizing gamma radiation for sterilization.

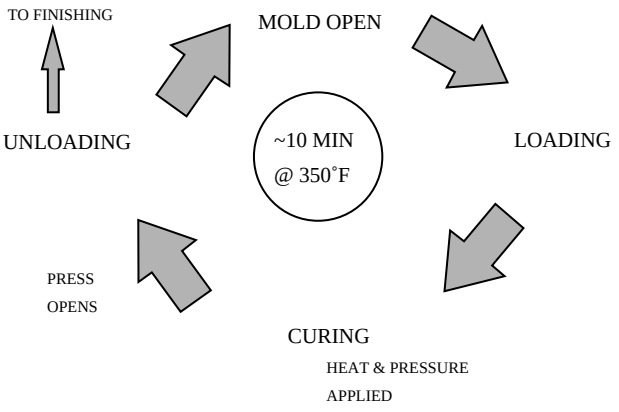


Fig. 3 Compression molding cycle.

2. *Ready to Use (RtU):* The process is identical to that used for RtS components except that the component manufacturer takes responsibility for component sterilization and the sterilized components are received by the drug or device manufacturer. No additional component processing is required before use.

Both processes typically require extensive validation by the component manufacturer, a description of the process in a Drug Master File (DMF), quality audits by customers, and perhaps FDA approval before RtS or RtU components are utilized. Nevertheless, RtS and RtU are trends that are moving rapidly; most major rubber component manufacturers now market RtS components (3). A list of pharmaceutical rubber manufacturers is shown in Table 7.

STERILIZATION OF RUBBER COMPONENTS

Heat, radiation, and sterilizing gases may be used to sterilize rubber components. However, components, especially vial stoppers, are most frequently sterilized by pressurized steam (autoclaving), a highly effective method and probably the most reliable of available methods when an F_0 value of at least 8 min is reached (4). However, the poor thermal conductivity of rubber and the relatively large mass of wet stoppers placed in a stainless steel container for sterilization require a careful validation of the process. Assurance must be obtained that the moist heat penetrates throughout the mass of stoppers so that every stopper receives a dose equivalent to a minimal F_0 of 8 min. However, rubber closures subjected to elevated temperatures or extended heating even at moderate temperatures degrade or revert, which is most frequently evidenced by stickiness. Therefore, the application of moist heat must be controlled because this degradation is most likely to be greatest at the outer layers of the mass of stoppers. This undesirable effect can be markedly reduced by distributing the stoppers in a shallow tray or otherwise reducing the mass, thus making it possible to reduce the thermal cycle time and the applied heat. Cycle times of 121°C for 30–60 min are usually well tolerated by rubber components made from butyl or halobutyl rubbers. Natural and isoprene rubbers are less tolerant. Increasing the sterilization temperature above 121°C or the time above 60 min is not recommended unless components have been tested to assure that no significant degradation will take place. Dry heat sterilization or drying of components above 105°C is also not recommended without prior testing. Testing may include inspection of the surface for cracks or tackiness, swelling studies to determine state of cure, functional tests such as coring and reseal, and chemical tests such as the United States Pharmacopoeia (USP) protocol or extraction studies performed before and after the sterilization cycle.

Under the usual autoclaving conditions, moist heat does not destroy pyrogens. For closures to be pyrogen-free, a final rinse with WFI before sterilization is necessary.

Ethylene oxide, a sterilizing gas, may be used to sterilize rubber components when they are part of a medical device; however, the gas is readily absorbed by the rubber and sufficient time must be allowed after sterilization for the concentration of residual ethylene oxide to dissipate to acceptable levels (5, 6).

Radiation sterilization, by either gamma or e-beam, also may be utilized to sterilize rubber components. However, some elastomers, such as butyl, chlorobutyl, and bromobutyl, do not tolerate high doses of radiation, while others, such as natural, isoprene, neoprene, and nitrile rubbers are readily radiation-sterilized without degradation (7, 8). The challenge with radiation sterilization of rubber components in bulk (i.e., cartons or bags) is to obtain a uniform dose of radiation throughout the entire package—enough of a dose to assure the desired sterility assurance level (SAL), usually 10^{-6}, without degrading the components, especially those nearest the radiation source. There are generally two approaches that can be followed. One is to target a uniform dose of 25 kGy, which is generally accepted to assure sterility, while the other is to follow the ANSI/AAMI/ISO 11137:1994 standard and target a dose of radiation that is dependent on the bioburden of the components (9). The first approach is usually overkill but may be acceptable for radiation-resistant rubbers. The second approach usually results in lower doses applied, which may be critical with butyl and other rubbers that are not so radiation resistant. There are several necessary steps if the ANSI/AAMI/ISO standard is used. These are:

- Selection of the SAL, usually 10^{-6}
- Determination of the average bioburden from samples taken from three consecutive production lots
- Establishment of the Verification Dose. This is the dose in kGy found in Table B.1 of the standard that will give a SAL of 10^{-2}
- Confirmation of the Verification Dose by irradiating 100 components and testing each for sterility. No more than two positives are permitted
- Establishment of the Sterilizing Dose from Table B.1 of the standard
- Dose mapping, using dosimeters, on a shipping container filled with components. Irradiate and determine the maximum and minimum doses (D_{max} and D_{min}) received in the container
- Calculation of the Target Dose by multiplying the Sterilizing Dose by the ratio, D_{max}/D_{min}. The Target Dose is typically increased 6% or more to account for dosimeter error and to add additional sterility assurance.

TESTS AND STANDARDS

In-Process Tests

Several tests may be performed on unvulcanized rubber or on standard-shaped test specimens to measure the properties of a rubber compound (10). These include the following:

1. *Rheometer measurements* measure cure and cure rate characteristics of the rubber. The component

Table 7 Pharmaceutical rubber packaging component manufacturers

Name	Symbol[a]	Address	Phone	Website or e-mail address
Abbott Laboratories	AB	268 E. Fourth Street, Ashland, OH 44805, USA	+419-282-5378	www.abbott.com
AL group Wheaton	AL	618 Beam St., Salisbury, MD 21801, USA	+410-546-6441	www.alcanpackaging.com
Bryant Rubber Corp.	BR	1112 Lomita Blvd., Harbor City, CA 90710, USA	+310-530-2530	www.bryantrubber.com
Daikyo Seiko, Ltd.	DS	38-2, Sumida 3-Chome, Sumida-Ku, Tokyo 131, Japan	+81-3-3614-5461	
Helvoet Pharma	HP	Industrieterrein Kolmen 1519, B-3570 Alken, Belgium	+32-11-59-08-00	www.helvoetpharma.com
Itran-Tompkins Rubber Corp.	IT	375 Metuchen Rd., South Plainfield, NJ 07080, USA	+908-754-8100	www.itranrubber.com
Kokoku Rubber Inc.	KO	1450 E. American Lane, Zurich Towers, # 1545, Schaumburg, IL 60173, USA	+847-517-6770 Ext 12	www.kokokurubber.com
Lexington Medical	LR	663 Bryant Blvd. Rock Hill, SC 29732, USA	+803-366-7036	
The Plasticoid Company	PL	249 High Street, Elkton, MD 21921, USA	+410-398-2800	www.plasticoid.com
Samsung Medical Rubber Co., Ltd.	SA	474-4, Mokne-Dong, Ansan-City, Kyunggi Province, Korea	+82-345-491-8071	www.smrco.co.kr
Seal Line S.p.A.	SL	Via Bernarde, 7, 36040 Montegaldella (VI), Italy	+39-0444/737221	Sealline@keycomm.it
Stelmi Trading International	ST	121, avenue Jean Mermoz, BP-93, F-93127 La Courneuve Cedex, France	+(33)-1-49-92-64-00	www.stelmi.com
West Pharmaceutical Services	WP	101 Gordon Drive, Lionville, PA 19341, USA	1-800-231-3000	www.westpharma.com

[a]Abbreviation for reference use in this chapter only.

manufacturer performs this test on unvulcanized rubber. The rheometer measures the viscosity of the rubber as a function of time at a constant temperature. As time increases, the degree of cure or cross-linking increases and thus the viscosity increases.

2. *Durometer hardness is* measured on tests specimens that meet specific standards for shape and thickness (11). Durometer hardness is usually measured using the Shore A scale, which measures relative hardness on a scale of 0 to 100 units. Most rubber components for medical use are found in the 35–60 range with 40–50 typical for rubber vial stoppers. Durometer Hardness may be measured on some actual components if they have a sufficiently large flat surface and thickness, i.e., 28–32 mm IV stoppers.
3. *Compression set is* commonly used as a measure of the dimensional recovery of a rubber compound after compression at a defined level, usually 25%, at a specified time and temperature, usually 24 h at 70°C (12). High compression set values are associated with rubber that "takes a set" or loses its ability to spring back after compression. Low compression set is important for rubber closures and syringe plungers that are heat sterilized while under compression and remain under compression for long periods of time before use but must remain elastic and resilient to maintain seal integrity. Compression Set is measured on dimensionally defined test specimens.
4. *Tensile, modulus, and elongation* are measures of the strength of a rubber compound (13). They are measured on bow tie-shaped specimens that are clamped in a tensile measuring apparatus and stretched.
5. *Water vapor and oxygen transmission (WVT and O_2T)* are commonly measured on thin-film specimens. Butyl and halobutyl compounds have very low WVT and O_2T rates, while rates for natural and isoprene rubbers are higher and for silicone even higher.

Finished Component Tests

Finished component tests may be divided into three categories: those used as routine identity and/or quality control tests, those tests recommended or mandated by government, standards, and compendial groups, and those test that are part of the larger rubber component acceptance and drug/device approval process. In many instances, a test may fall into more than one category.

Identity and quality control tests (14, 15)

Percentage ash is a measure of the nonvolatile materials in a rubber formulation, such as clays and other fillers.

Specific gravity is a measure of the type and quantity of fillers in a formulation.

An *infrared spectrum* of a compound pyrolysate identifies the elastomer qualitatively (natural, butyl, etc.).

An *ultraviolet (UV) spectrum* of an aqueous rubber extract identifies and quantifies the antioxidants, curing agents, accelerators, and other UV-absorbing species extracted from the compound.

Percentage swelling in an organic solvent is a measure of the degree and consistency of cure or cross-linking that determines the physical and functional properties of a component.

These five tests may be used to characterize a rubber formulation or serve, either individually or in combinations, as quality control tests.

Compendial, standard, and government tests

The most influential of these test protocols are the USP (16), the *European Pharmacopoeia* (EP) (17), the *Pharmacopoeia of Japan* (JP) (18), the Organization for International Standardization (ISO) (19), and the Parenteral Drug Association (PDA) (15, 20). USP<381>, Elastomeric Closures for Injections, contains five chemical tests and two biological tests. Closures must meet the biological requirements but there are no current specifications for the chemical tests. All USP chemical tests are commonly performed on aqueous extracts but isopropyl alcohol and the drug product vehicle are also permitted. A brief description of the USP<381> tests follows (21).

Turbidity. The clarity of the closure extract is measured with a nephelometer with appropriate standards. Turbidity is a measure of the insoluble extractables from a closure and is affected by the type and amounts of ingredients in a formulation, pretreatments such as washing, extractions, sterilizations, and degree of cure.
Reducing agents. Organic extractables oxidizable by iodine are determined in this procedure. It is affected by the same variables as turbidity.
Heavy metals. Extractable lead as well as other metals, such as zinc and cadmium, are determined colorimetrically or by atomic absorption.
pH change. The pH of the extract is a measure of the acidic and alkaline water-soluble extractables from a compound.
Total extractables. The sum of the inorganic, organic (nonvolatile), soluble, and insoluble extractables is measured in this test. The weight of total extractables is an indication of the "cleanliness" of a formulation.
Biological tests. USP 24 lists two levels of biological tests—the in vitro tissue culture test and the in vivo systemic injection and intracutaneous tests. A parenteral

closure must pass either type of test to meet USP requirements.

The application of numerical specifications to the USP <381> chemical tests is under discussion and probably will become effective in USP 24 via a supplement. The JP, EP, and ISO have specifications for rubber closures and these test protocols are compared with the USP in Table 8. Not all pharmacopeias and standards groups designate the same tests; therefore, it is important to consult a wide spectrum of references to design a test protocol for specific applications and geographical submissions. Of the four protocols compared, the JP is the most stringent in terms of limits for extractables. The USP, EP, and ISO test protocols are based on a specific closure "area" per volume of water in the extraction step. The JP test protocols, on the other hand, are based on a specific "weight" of closures per volume of water. This difference makes it more difficult for smaller closures than for larger closures in the same rubber compound to meet JP specifications; i.e., 13-mm closures will be less likely to meet JP specifications than 20-mm closures, and 20-mm closures are less likely than 28-mm closures to meet JP specifications.

Although packaging components, such as vial closures, syringe plungers, and needle shields, may meet all compendial and accepted standards, this does not mean that they will be acceptable for use with any specific drug or device. Specific evaluation tests must be performed for that purpose. Compendial and standard tests should be regarded as the first necessary but not sufficient hurdle in the race to gain approval of a component for use with a drug or device.

Specific tests for component evaluation and regulatory approval

There are three requirements for a rubber component:

1. Compatible with the drug
2. Meets functional requirements
3. Provides closure-container seal integrity

Many factors influence the choice of a rubber compound for a particular drug, the most important of which is the solvent vehicle. If the solvent vehicle is an aqueous material, then a butyl, natural, or EPDM may be used. If the solvent vehicle is an oil, then a neoprene or nitrile is utilized.

Configuration is also important and is determined by the required function. A lyophilization stopper, designed to keep out moisture, almost certainly requires a butyl formulation, while a vial stopper for aqueous-based solutions could be formulated from isoprene rubber.

Some preservatives are especially reactive with rubber. Bromobutyl rubbers, but not chlorobutyls, are recommended for drug formulations that contain chlorobutanol. A pH that is either very low or very high affects rubber formulations more than a pH in the range of 5–8. Buffer systems may also affect the choice of rubber formulations. Materials such as phosphates not only attack the rubber at high pHs but also may attack glass as well.

Metallic sensitivities affect compatibility, as drug formulations that are sensitive to divalent cations, such as calcium, zinc, or iron, may not be able to use certain rubber compounds that are cured or pigmented with these materials.

An obvious factor is the need for oxygen or moisture vapor protection. A butyl-based compound is normally chosen whenever protection from materials transmitted either into or from a drug product is required.

When it comes to color preference, most rubber manufacturers of closures used for drugs prefer to use three pigments: iron oxide to produce reds, carbon black for blacks, and titanium dioxide for whites; combinations of these are used for pinks and grays. Organic materials used as pigments are not generally acceptable since they are not very heat stable and are generally more toxic than the three pigments mentioned.

Choice of sterilization method is extremely important in choosing a rubber formulation. Many heat-sensitive drugs, such as proteins, are packaged aseptically; that is, the rubber closure, the vial, and drug are sterilized separately, and then all three items are brought together in a sterile environment to form the final package. The FDA, however, encourages terminal sterilization. In this method, the three materials are brought together and then the entire package, the drug in contact with the vial and closure, is sterilized by heat. This method is much more demanding on the closure than aseptic processing.

Radiation (Co-60) is used to sterilize many rubber items, especially those used in devices. The effect of gamma radiation on rubber closures is a function of the elastomer, dose, and postirradiation time. NR and isoprene are much more resistant to irradiation effects than butyl.

To give the drug manufacturer a high degree of assurance that the closures being investigated for a possible package will be acceptable, a prescreening procedure is commonly used by component suppliers. In this procedure, information and a sample of the drug are obtained from the drug manufacturer. Then three to five possible closures, along with an inert control stopper (a Teflon® plug or coated closure), are used to package vials of the drug. The closures are put onto the drug-containing vials using an exaggerated closure area-to-volume ratio (2× to 3× the normal ratio). Vials are stored at higher and/or lower temperatures than

Table 8 Comparison of USP, EP, JP, and ISO test protocols for rubber closures

	USP[a]	EP[b]	JP[c]	ISO[d]
Test types and limits				
Chemical tests	Y	Y	Y	Y
Biological tests	Y	N	Y	N
Functional tests	N	N	N	Y
Test limits	Y, only on Biological Tests	Y	Y	Y
Specific tests				
Alkalinity/pH	Y	Y	Y	Y
Ammonia	N	Y	N	Y
Appearance/turbidity	Y	Y	Y	Y
Ash, total	N	Y	N	Y
Conductivity	N	N	N	Y
Container-closure integrity	N	N	N	Y
Design/dimensional specifications	N	N	N	Y
Elasticity	N	Y	N	Y
Extractable zinc	N	Y	Y	Y
Foam	N	N	Y	N
Fragmentation/coring	N	N	N	Y
Halides	N	N	N	Y
Hardness	N	N	N	Y
Heavy metals	Y	Y	N	Y
Hemolysis	N	N	Y	N
Intracutaneous injection	Y	N	N	N
IR of pyrolysate	N	Y	N	Y
Particulate matter	N	N	N	Y
Penetrability	N	N	N	Y
Pyrogens	N	N	Y	N
Reducing substances	Y	Y	Y	Y
Residue on evaporation	Y	Y	Y	Y
Resistance to steam	N	N	N	Y
Self sealing	N	N	N	Y
Storage	N	N	N	Y
Systemic injection	Y	N	Y	N
Tissue culture	Y	N	N	N
Total Cd and Pb	N	N	Y	N
UV absorbance	N	Y	Y	Y
Volatile sulfides	N	Y	N	Y

[a]From Ref. 16, Section <381>.
[b]From Ref. 17, Section 3.1.12.
[c]From Ref. 18, Section 49.
[d]From Ref. 19, ISO 8871, ISO 8362-2 & 8362-5, ISO 8536-2 & 8536-6.

the drug package will normally experience in the upright, inverted and on-side positions.

An inert control stopper should be used since a drug may be stable against glass but not against uncoated rubber. Only when an inert control is used will it be possible to determine whether the rubber and/or glass vial is the cause of the drug instability. Ampoules do not make good controls for the prescreening of drugs in vials since the glass for vials may be different from that used for ampoules.

Table 9 summarizes the important drug compatibility factors that must be considered when choosing a rubber component for a specific drug/device application. These factors along with the functional and seal integrity requirements can be used to write specifications for components. The packaging engineer, as with the rubber compounder, faces the challenge of choosing a compound that best meets the overall requirements but, only at best, provides a balance of all the actual chemical and functional needs. For example, an engineer may choose

an isoprene vial closure because multiple punctures with a large cannula are required. Isoprene will provide the low coring and excellent reseal required. But the engineer may give up some shelf life since isoprene is a poor oxygen barrier. Choosing a butyl closure would give additional shelf life due to its better barrier properties, but coring and reseal would not be acceptable. Closure compound choice is always a give-and-take proposition where drug/device requirements must be prioritized before the choice of a rubber compound can be made. Table 10 lists important physical and chemical properties of elastomers (22).

There are four general types of closure–drug interactions:

1. Adsorption occurs when a drug is concentrated at the surface of a closure or vial.
2. Absorption occurs when a drug material is dispersed in the closure matrix.
3. Permeation is the transmission of a drug ingredient through a closure into the atmosphere or transmission of an outside material into the container.
4. Leaching is the process by which closure ingredients are extracted into the drug product.

All four of these interactions commonly occur. No rubber compound is absolutely inert to a drug. In many cases, the extent of the particular interaction is extremely small and may not be measurable, but generally all four are occurring, albeit at a low rate. With proteins, adsorption can be a problem. Many proteinaceous materials made by the biotechnology industry are highly adsorbent onto rubber surfaces and their potency may be readily lost. Other drugs products, especially ones that are very acidic or basic, may attack the stopper and cause the extraction of rubber compound ingredients. Common leachables from rubber closures include low molecular weight elastomer fragments, metal ions, antioxidants, plasticizers, lubricants, curing agents, and accelerators. The rate and relative importance of these four interactions determines the degree of compatibility or incompatibility of a stopper with a drug product.

In May 1999, the FDA issued an updated guidance entitled "Container Closure Systems for Packaging Human Drugs and Biologics—Chemistry, Manufacturing and Controls Documentation," that listed in tables the packaging information that should be submitted in an application (23). The guidance divides the information into four sections:

1. *Description*—Overall general description of the container-closure system plus specific information on suppliers, materials of construction, and postmanufacturing treatments.

Table 9 Drug compatibility factors affecting the choice of rubber component

Liquid or solid?
Liquid
1. Aqueous—pH, preservative, buffer cosolvent?
2. Oil—Vegetable or Mineral?
Solid
1. Lyophilized or powder fill?
Configuration?
Need for O_2, H_2O, CO_2 protection?
Drug type?
Metallic sensitivities?
Method of closure and package sterilization?
Color preference?

2. *Suitability*—This section prescribes that tests must be done to assure protection of the drug product, safety of the packaging component material, compatibility of the component with the drug product, and performance of the component.
3. *Quality control*—The rubber component manufacturer's release criteria and drug packager's acceptance are found in this section. Also recommended is a method to monitor the consistency in composition of elastomeric components such as periodic extraction profiles.
4. *Stability*—Testing of the drug product using the packaging component is required. Unlike compendial tests that utilize water for extraction studies of the packaging component, the complete drug product is utilized in these stability studies.

This guideline advocates more information on rubber extractables and the proper use of DMFs.

Knowledge of extraction data from elastomeric components refers not only to the broad (and usually nonspecific) type of extractable data generated in USP<381> testing, but also to the identification and quantification, where necessary, of specific extractable species. Example of nonspecific extractables include turbidity, reducing agents, heavy metals, pH change, and total extractables-; They all measure broad types of extractables. Specific extractables include inorganics, such as zinc or lead and organics, such as PNA, stearic acid, nitrosamines, tetramethylthiuram disulfide, or 2,6-di-*tert*-butyl-4-*sec*-butyl phenol. Both liquid (HPLC) and gas chromatography (GC) are well suited for this purpose (24). Drug/device producers who utilize elastomeric packaging components require information from their suppliers on extractables (extractable profiles), including test methods, that are generated in water at various pH values (i.e., 3, 7, and 10) and in organic solvents such as isopropanol.

Table 10 Physical and chemical properties of elastomers[a,b]

	Common name of elastomer (chemical name)								
Property	**Butyl/halobutyl (Isobutylene-isoprene copolymer)**	**Natural/ Isoprene (cis-1,4-polyisoprene)**	**Neoprene (polychloroprene)**	**Nitrile (butadiene-acrylonitrile copolymer)**	**Silicone (polydi-methysiloxane)**	**Fluoro-elastomers (fluoro-rubber)**	**Urethane (polyester isocyanate)**	**EPDM (ethylene propylene diene monomer)**	**Butadiene (*cis*-Polybutadiene)**
Abrasion resistance	Fair	Good	Fair	Good	Fair	Good	Excellent	Good	Fair
Compression set	Poor	Excellent	Good	Good	Poor	Good	Excellent	Good	Good
Coring	Fair	Excellent	Good	Fair	Poor	N.D.[c]	Excellent	Fair	Fair
Gas transmission resistance	Excellent	Good	Fair	Good	Poor	Good	Poor	Fair	Fair
Heat resistance	Excellent	Good	Good	Good	Excellent	Excellent	Poor	Very Good	Good
Machine-ability	Poor	Good	Fair	Good	Fair	N.D.	Fair	Fair	Good
Moisture vapor resistance	Excellent	Good	Fair	Fair	Poor	Good	Poor	Fair	Fair
Ozone resistance	Excellent	Poor	Good	Fair	Excellent	Excellent	Good	Good	Fair
Radiation resistance	Fair to Poor	Good	Good	Good	Fair to Good	Fair to Good	Fair	Fair	Poor
Resilience	Poor	Excellent	Good	Good	Good	Fair	Good	Good	Good
Shelf-life	Good	Fair	Good	Fair	Excellent	Excellent	Excellent	Excellent	Fair
Solvent resistance									
Acid, dilute	Good	Good	Good	Good	Fair	Fair	Poor	Good	Fair
Aliphatic solvents	Poor	Poor	Good	Poor	Poor	Excellent	Excellent	Good	Poor
Alkali, dilute	Good	Good	Good	Good	Good	Good	Poor	Good	Fair
Animal oil	Excellent	Poor	Good	Excellent	Good	Excellent	Excellent	Fair	Fair to poor
Aromatic solvents	Good	Good	Poor	Good	Poor	Excellent	Poor	Fair	Poor
Chlorinated solvents	Poor	Poor	Poor	Poor	Poor	Excellent	Good	Poor	Poor
Mineral oil	Poor	Poor	Good	Excellent	Fair	Excellent	Excellent	Poor	Poor
Vegetable oil	Excellent	Poor	Good	Excellent	Excellent	Excellent	Excellent	Fair	Fair to poor
Water	Excellent	Good	Fair	Good	Excellent	Good	Poor	Good	Good

[a]Ratings adapted from Ref. 22.
[b]Ratings expressed are typical for rubber compounds made from the elastomers; they can vary significantly from compound to compound.
[c]ND, not determined.

Armed with this information, they can look for extractables in their drug products.

Confidential packaging component information, such as the compound recipe, may be placed in a Type III DMF so that the FDA can review the information when it reviews the drug application (IND, NDA, ANDA, or BLA) (25). Most elastomeric compounds are filed at the request of a pharmaceutical manufacturer who has chosen to use the rubber closure in one or more drug packages or devices applications. The name of a rubber compound is associated with a precise recipe that designates specific ingredients and quantities. Once a rubber compound is filed in a DMF, no changes can be made in that compound without changing the DMF and notifying all customers on whose behalf the DMF was accessed and reviewed by the FDA. Since changes in a supplier's DMF may require additional stability studies by the drug manufacturer, changes are infrequent.

RECENT ISSUES AND DEVELOPMENTS

Latex Sensitivity

There are medical and regulatory issues surrounding the use of "latex rubber" due to allergic reactions that have resulted in medical emergencies. Even deaths have been noted (26, 27). There are two broad types of rubber—natural and synthetic. Several synthetic rubbers or elastomers are used for pharmaceutical components. These are listed in Table 10. However, there is only one type of commercial NR, which is derived from the rubber tree *Hevea Brasiliensis*. "Latex sensitivity" is associated only with NR and not with the synthetics, although other types of allergic reactions can result from contact with synthetic rubbers. NR is processed and used in two forms—liquid or latex rubber and solid or dry rubber, often referred to as crepe, SMR, and SIR. Specific proteins that are contained in both the latex and dry types cause the sensitivity to NR. Thus, the medical community and regulatory authorities have used the term "latex" for both forms of NR when "latex sensitivity" is discussed. Latex reactions reported in the literature have thus far been attributed to contact with components made from liquid rubber but not from dry rubber. Components made from liquid rubber are made by a dipping process that is best suited for thin-walled items such as gloves, condoms, and catheters. None of the typical rubber packaging components shown in Figs. 1 and 2 is made from latex rubber; —they are all made from dry rubber via a molding process. Many studies have been published regarding the allergic properties of latex and dry rubber (28, 29) and further studies are in progress to determine if exposure to these dry rubber components can cause allergic latex reactions (30).

There is a great deal of regulatory activity in an attempt to protect the public from unexpected latex reactions. In 1996, the USP proposed a change in section <381> that would prohibit the use of NR in elastomeric closures (31); however, it rescinded this change in April 1997, stating that closure manufacturers should instead devise latex protein limits. A test for the water-soluble protein content of elastomers, based on an ASTM test (2), was published as USP <836> but no specifications or limits were proposed (33). At the same time, the FDA published a final rule that made it mandatory to provide labeling statements on medical devices and packaging components that contain NR (34). This rule was later amended to exclude combination drug/device and biologic/device products such as rubber stoppers and plungers for prefilled syringes (35). The uncertainty about the allergic risk from dry NR components and pending regulations have significantly reduced the use of NR in packaging for new drugs and in devices. Substitutes such as isoprene and SBR rubbers are finding increased use.

Preprocessed Components

Preprocessed closures, commonly referred to as RtS or Ready for Sterilization and RtU or Ready for Use, are an unstoppable trend in pharmaceutical packaging. Information on the manufacturing of these products was described previously in this review. The purpose of preprocessed closures is to reduce total processing costs and improve closure characteristics. Typical RtS closure characteristics are as follows:

Endotoxin Level: < 1 EU/closure
Bioburden Level: < 2 cfu/closure
Silicone Level: 10–40 μg/closure
Visible Particulate Matter: < 20 particles in 25 to 50-μ range; < 2 particles in 50 to 100-μ range; < 1 particle over 100 μ.

Coating and Surface Treatments

Although the material science of rubber compounds has greatly improved, drug-closure-interactions and surface lubricity are problematic for packaging engineers. Surface modifications of closures are frequently necessary to meet acceptance standards set by the USP, EP, JP, and ISO as well as the expectations of regulatory authorities. In practice, both liquids and solids are applied to closure surfaces to minimize interactions and improve lubricity.

Table 11 Commercially available coated and surface treated components

Product name	Material	Primary use	% Surface coated	Supplier[a]
Abboclad	Fluorinated polymer solid film	Compatibility	Plug surface	AB
B2	Silicone, polymerized liquid	Lubricity	Top, plug or both surfaces	WP
Coated stopper	Parylene deposited solid film	Compatibility	Total	IT
Deposition coated stopper	Vapor deposition coated solid film	Compatibility	Total	AB
Flurotec	ETFE solid film	Compatibility	Top, plug or both surfaces	WP & DS
Omniflex plus	Solid fluoropolymer coating	Compatibility	Total	HP
R2	Polymer, nonsilicone solid	Lubricity	Total	ST
SAF	Silicone, high viscosity liquid	Lubricity	Total	HP
Slipcoat	Plasma deposited polymer solid	Lubricity	Total	AL

[a]See Table 7 for supplier information.

A compilation of commercially available coated and surface treated components is shown in Table 11 (36). Although these coating and surface treatments may add significantly to the purchase price of closures they often reduce the total drug product cost by providing the following benefits:

- Increased lubricity, which allows faster processing speeds
- Decreased drug–closure interactions, which permits the marketing of some products not compatible with uncoated rubber and better quality and longer shelf life for others
- Decreased particulate matter, which reduces the number of units rejected for visible particulate matter

Container-Closure Seal Integrity

The FDA Guidance on Container Closure Systems (Ref. May 1999 Guidance) lists sterility or container integrity as an important parameter to be considered in the section on Protection. Seal integrity tests can be done by both physical and microbial methods, but historically, sterility testing alone has been used. A 1998 FDA draft guidance discusses the replacement of the sterility test with an appropriate container-closure integrity test in the stability protocol, permitting an alternative to sterility testing for proving the continued capability of containers to maintain sterility (37). Kirsch et al. (38–41) published a series of four papers that studied mass spectrometry-based helium leak detection, microbial ingress, and vacuum decay and the correlation between these methods. The PDA also published an updated technical report that provides guidance for evaluating pharmaceutical package integrity (42), and Guazzo has published an excellent review article that outlines the advantages and limitations of current methods (43).

SUMMARY

Rubber packaging and device components are an important part of the overall medical delivery system. Without innovative packaging systems, modern drugs would not be available today. Advances in drug development have initiated research in new packaging and delivery systems while the availability of innovative packaging has led to the introduction of new drug therapies. Innovation, while containing costs and conforming to regulations, is the challenge for the 21st century.

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